UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/783,054	02/20/2004	Ashutosh Chilkoti	5405-318	6784

20792 7590 07/16/2010

MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

EXAMINER	
HELM, CARALYNNE E	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
07/16/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/783,054	CHILKOTI ET AL.	
	Examiner	Art Unit	
	CARALYNNE HELM	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-9,11-31 and 51-59* is/are pending in the application.

4a) Of the above claim(s) *3,15,20,22-27,52 and 54-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 4-9, 11-14, 16-19, 21, 28-31, 51, and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/27/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Note to Applicant: References to paragraphs in non-patent literature refer to full paragraphs (e.g. 'page 1 column 1 paragraph 1' refers to the first full paragraph on page 1 in column 1 of the reference)

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 7, 2010 has been entered.

Election/Restrictions

To summarize the current election, applicants elected the species where the article is an orthopedic implant, the protein-resistant head group is tri(sarcosine), and the surface portion comprises metal.

Claims 3, 15, 20, 22-27, 52, and 54-59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim.

NEW OBJECTIONS/REJECTIONS

Claim Objections

Claim 28 is objected to because of the following informalities: the recitation "csaid article omprising" appears to include a typographical error. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4-9, 11-14, 16-19, 21, 28-31, 51 and 53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods where the contacting occurs for approximately 26 days or less, does not reasonably provide enablement for the method of use as claimed when the linking layer is an alkanethiol terminated initiator on gold and the contacting occurs for more than 26 days in a biological fluid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a

disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to methods of utilizing devices with non-fouling coatings that resist protein binding upon contacting with a biological fluid. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Flynn et al. (Langmuir 2003 19:10909-10915). Flynn et al. provide data that address the stability of alkanethiol self-assembled monolayers on gold that carry non-fouling terminal groups. After approximately 21 days in blood serum, the stability of the

monolayer was compromised such that it lost much of its protein resistance (see page 10914 column 2 paragraph 1). Applicants also highlight this instability in their arguments. While Flynn et al. suggest that crosslinked non-fouling terminal groups may provide longer duration stability of the thiol based monolayers, they do not provide a predictable means of stabilizing their uncrosslinked taught layers. Furthermore, applicants do not contemplate modifying their alkanethiol supported monolayers or the crosslinking of the non-fouling moieties to prolong the stability of the coating.

2. The breadth of the claims

The claims include a boundless duration of exposure of the claimed alkanethiol supported polymer brushes while still achieving protein resistance. Since these layers are known to be unstable, at some point during this exposure these monolayers will fail completely. At such point, the protein resistance would end and the device would no longer function as claimed.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for how to practice the invention as claimed beyond the 26 days exemplified. While it is not evident that 26 days of exposure to blood would necessarily render the claimed polymer brush coating inoperative, no evidence or guidance has been provided by applicants to instruct one of

ordinary skill in the art how to sustain a functional coating beyond this time point. Given the teachings of Flynn et al., one or ordinary skill in the art would expect the decomposition of the alkanethiol based coating over time. Although applicants acknowledge the instability of these layers they do not instruct one of ordinary skill in the art how to ameliorate this limitation such that the full breadth of the invention can be practiced.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art of stabilizing an alkanethiol supported coating as described by the instant invention, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed method could be predictably practiced as inferred by the claims and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The four factual inquiries of Graham v. John Deere Co. have been fully considered and analyzed in the rejections that follow.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 4, 11-14, 21, 28-31, 51, and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mittleman ("Adhesion to Biomaterials." Bacterial Adhesion Molecular and Ecological Diversity. Ed. Madilyn Fletcher New York: Wiley-Lias Inc.

1996. 89 and 108-109), Bialk et al. (Colloids and Surfaces A Polymer Chemistry 2002 198-202:543-549)., Zhang et al. (previously cited), Ejaz et al. (Macromolecules 2000 33:2870-2874), and Chapman et al. (previously cited).

Mittleman teaches that orthopedic implants are colonized by bacteria via blood which is termed hematogenous seeding (see figure 4.4 and page 109 paragraph 2). He goes on to teach that the consequences of such colonization are severe (see page 109 paragraph 2). Since infections of orthopedic implants can require additional surgeries to cure the infection (e.g., replacement of implant and/or remediation of infection) the artisan of ordinary skill would have desired an alternate avenue to reduce the likelihood of infection.

Bialk et al. teach the grafting of polymer chains from the surface of medical implants to improve their biocompatibility (e.g., protein or bacterial adhesion) (see page 543 columns 1 and 2). Bialk et al. teach that initiator molecules are bound to the surface (linking layer) (see page 543 column 2). In addition, vinyl containing monomers are envisioned for such polymers (see abstract).

Zhang et al. teach polymer brushes utilized to resist protein adhesion on implant surfaces (see page 691 column 1 paragraph 10). Specifically these polymers are composed of monomers of methacryloyloxyethyl phosphorylcholine, an acrylate monomer with a coupled phosphorylcholine group, and butyl methacrylate (see page 691 column 2 paragraph 1 and page 700 column 1 paragraph 2; instant claim 11).

Ejaz et al. teach the covalent binding of an initiator to a substrate surface to facilitate a surface-initiated polymerization (see page 2871 column 1).

Chapman et al. teach non-fouling coatings on devices that resist the adhesion of bacteria and proteins (see paragraphs 9 and 10). Chapman et al. teach such coatings for articles that are in-dwelling, such as artificial bone or joint replacements (orthopedic implant) as well as metals for their constituent material (see paragraph 64; instant claim 21). Such devices are known to be implanted for more than one day when utilized as intended (see instant claims 29, 31, and 51). These coatings include polymers grafted to the device surface (see paragraph 153; instant claim 7). This polymer contains several head groups (branches) that resist the adsorption of proteins and bacteria (see paragraph 153 and 162). Both phosphorylcholine and tri(sarcosine) (kosmotrope) are taught head groups; however, tri(sarcosine) is more effective at resisting bacterial adhesion than phosphoryl choline (see figure 5; instant claim 12-14).

In light of the teachings of Bialk et al., it would have been obvious to one of ordinary skill in the art at the time of the invention to graft a polymer that resists bacterial adhesion from the surface of a joint replacement prior to its implantation. Grafting a methacrylate based monomer (e.g., MPC) from the device surface via a covalently bound initiator, as taught by Bialk et al., Zhang et al. and Ejaz et al., would also have been obvious since its side chains were known to resist bacterial adhesion. Given the teachings of Chapman et al., replacement of the phosphorylcholine side chain with tri(sarcosine) due to its better bacterial resistance would have been an obvious modification of this monomer and generated the recited device. Finally, long term implantation of this joint replacement as is intended and contacting it with blood during the course of this implantation would have been obvious and had a reasonable

expectation of success for repulsion of bacterial adhesion. Therefore claims 2, 4, 11-14, 21, 28-31, 51, and 53 are obvious over Mittleman in view of Bialk et al., Zhang et al., Ejaz et al., and Chapman et al.

Claims 17 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mittleman in view of Bialk et al., Zhang et al., Ejaz et al., and Chapman et al. as applied to claims 2, 4, 11-14, 21, 28-31, 51, and 53 above, and further in view of Allbritton et al. (US PGPub No. 2005023748) and Leckband et al. (previously cited).

Mittleman in view of Bialk et al., Zhang et al., Ejaz et al., and Chapman et al. make obvious the method instant claim 28 where the device a metallic orthopedic device to which is attached a polymer brush composed of vinyl core monomers with tri(sarcosine) as head groups on its bristles (see instant claim 28). This modified reference does not explicitly teach the surface density of polymer.

Allbritton et al. teach surface grafted polymers to modify the surface of medical devices and confer desired properties (see paragraph 12). Particular monomers that resist protein adhesion are chosen for surface initiated polymerization (see paragraph 42). Allbritton et al. go on to teach various grafting densities for these monomers that include polyethylene glycol monomethoxyl acrylate (see paragraphs 34 and 42). Specifically, grafting densities from approximately 5 $\mu g/cm^2$ (50 mg/m^2) to 60 $\mu g/cm^2$ (600 mg/m^2) are taught (see figure 4A and paragraph 24; instant claim 17).

Leckband et al. teach polymer brushes on a substrate as a protein resistant surface (see abstract). In particular, Leckband et al. discuss that the graft density

(polymer surface density) is a key parameter in controlling the degree of protein adsorption retardation (see page 1143 paragraph 4). Leckband et al. also teach that this density is optimized based upon the target environment (e.g. size, geometry and concentration of proteins) (see page 1143 paragraph 4). Thus in view of the teachings of Allbritton et al. of polymers with functional groups that were taught by Chapman et al. to function similarly to tri(sarcosine), it would have been well within the purview of one of ordinary skill in the art to optimize the grafting density of the polymers of Mittleman in view of Bialk et al., Zhang et al., Ejaz et al., and Chapman et al. based upon the teachings of Allbritton et al. Therefore claims 17 and 28 are obvious over Mittleman in view of Bialk et al., Zhang et al., Ejaz et al., Chapman et al., Allbritton et al, and Leckband et al.

Claims 8-9 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mittleman in view of Bialk et al., Zhang et al., Ejaz et al., and Chapman et al. as applied to claims 2, 4, 11-14, 21, 28-31, 51, and 53 above, and further in view of Guan et al.

Mittleman in view of Bialk et al., Zhang et al., Ejaz et al., and Chapman et al. make obvious the method of instant claim 28. This modified reference does not explicitly teach that the polymerization is carried out via atom transfer radical polymerization.

Guan et al. teach that although it is know to polymerize vinyl monomers via free radical polymerization, atom transfer radical polymerization is also a viable means of polymerizing these same monomers (see column 1 lines 58-59 and column 2 lines 10-

19). Thus as known options within their technical grasp, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ atom transfer radical polymerization or free radical as the polymerization method in the invention of Mittleman in view of Bialk et al., Zhang et al., Ejaz et al., and Chapman et al. where vinyl monomers are used as the core group. Therefore claims 8-9 and 28 are obvious over Mittleman in view of Bialk et al., Zhang et al., Ejaz et al., Chapman et al. and Guan et al.

Claims 2, 4-7, 9, 11-14, 16, 18-19, 21, 28-31, 51, and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chapman et al. view of Hawker et al. (previously cited), Zhang et al., Morgan (US Patent No. 6,325,628) and Flynn et al.

Broadly, the invention of claims is a method of using a device (article) with a coating of polymer brushes on its surface that are attached to the device surface via a linking layer. These polymer brush bristles have protein resistant groups (kosmotropes) that confer protein resistance to the surface of the device. Chapman et al. teach this concept where their coating resists protein and bacterial adhesion (see figure 1 and paragraphs 114-117; instant claim 1). A self assembled monolayer of alkanethiol is formed on an article that is coated with gold (see paragraph 153 and 159; instant claims 2, 4 and 6). The exposed end is converted into a reactive functional group (initiator terminated alkanethiol) such that a polymer can be grafted (see paragraph 153; instant claim 7). This polymer contains several head groups (branches) that resist the adsorption of proteins and bacteria (see paragraph 153 and 162). Chapman et al. teach such coatings for articles that are in-dwelling, such as artificial bone or joint

replacements (orthopedic implant) (see paragraph 64; instant claim 21). Chapman et al. also teach self assembled monolayers that display different protein and bacteria resistant head groups. Tri(sarcosine) is in the set demonstrated to be particularly effective (see figures 4-5 and paragraph 144; instant claims 12-14). Chapman et al. go on to teach that in addition to protein and bacteria resistance, their polymer layers can be further modified by covalently attaching ligands that bind specific biomolecules (see paragraph 124; instant claim 18-19). Protein molecules as well as peptides are particularly envisioned as these ligands (see paragraph 121; instant claim 18). Since a receptor is a chemical structure that provides a site of attachment, these envisioned proteins qualify as receptors (see instant claim 19). Upon exposure to fluid with biomolecules, adsorption of general biomolecules (e.g. protein) and bacteria is resisted such that binding of those biomolecules for which the ligand is specific occurs (see paragraph 124; instant claim 32). The *in vivo* contacting of the device of Chapman et al. with biological fluids is clearly envisioned in their contemplation of in-dwelling medical devices as substrates for their taught coating (see paragraph 42).

In view of the teachings of Chapman et al., it would have been obvious to one of ordinary skill in the art at the time of the invention to select tri(sarcosine) as the protein and bacteria resistant head group to include in the surface bound polymer of their invention, where an orthopedic implant is the coated article and an alkanethiol layer linking the polymer to the article substrate. Since the use of a device for its intended purpose is obvious, the contacting of such a device to a biological fluid such that selective binding can occur to the attached ligands while repelling non-specific adhesion

would also have been obvious based upon the teachings of Chapman et al. This reference does not explicitly teach that the orthopedic implant is a dental prosthesis, that the polymer is formed of monomers with a vinyl core monomer group and a protein resistant head group coupled thereto, produced via surface initiated polymerization, or that the linking layer is patterned on the substrate.

Morgan teaches a dental implant with a threaded region that is composed of biocompatible material (e.g., titanium) and anchored into cortical bone (orthopedic implant) (see column 2 lines 28-35; instant claims 21 and 53). The implant is taught to be temporary, remaining implanted for four to six weeks (*in vivo* contacting with blood) (see column 1 lines 55-67; instant claims 28-31 and 51).

Zhang et al. teach polymer brushes utilized to resist protein adhesion on implant surfaces (see page 691 column 1 paragraph 10). Specifically these polymers are composed of monomers of methacryloyloxyethyl phosphorylcholine, an acrylate monomer with a coupled phosphorylcholine group, and butyl methacrylate (see page 691 column 2 paragraph 1 and page 700 column 1 paragraph 2; instant claim 11). Chapman et al. teach phosphorylcholine as an envisioned protein resistant head group whose performance in this capacity was not as good as tri(sarcosine) (see Chapman et al. figure 5).

Hawker et al. teach polymer brush patterns built from a self assembled monolayer on a substrate (see abstract; instant claims 38). In particular, a substrate surface that can be composed of a variety of envisioned materials (e.g. gold or tungsten) serves as the base for the polymer (see column 8 lines 9-18). Subsequently a

compound (linking layer) containing a group reactive with the substrate surface on one end and providing an initiator on the other end is applied to the surface (see column 8 lines 56-67 and column 9 lines 27-29). The material is then contacted with a polymerizable composition composed of monomers that sequentially form polymers at these initiation sites (see column 9 lines 60-64). One preferred technique utilizes an initiator that generates a free radical polymerization and vinyl monomers (see column 10 lines 10-17; instant claims 9, 28, and 51). The resulting polymers are taught to be between 28 and 38 nm in length (see figure 3; instant claims 16 and 48). This technique is taught in particular in the production of patterned surfaces, where the initiator containing molecules are placed in particular locales on the substrate (see column 8 lines 53-64; instant claims 5 and 37). In one example, Hawker exemplifies the compound that makes up the linking layer as an initiator terminated alkanethiol that forms a patterned or continuous self assembled monolayer (column 13 lines 46-50 and 58-63; instant claims 4-7 and 36-39).

Since Chapman et al. and Zhang et al. teach particular chemical moieties on medical device surfaces to resist adsorption of undesired biological species upon implantation, it would have been obvious to one of ordinary skill in the art to combine their teachings. In addition, it also would have been obvious to combine the teachings of Chapmen et al. and Hawker et al. because both teach surface bound polymeric coatings attached via self assembled monolayers of reactive alkanethiol groups on metallic surfaces. Further, it also would have been obvious to this ordinarily skilled artisan to select the dental implant of Morgan as an orthopedic implant suitable for the

invention of Chapman et al. Based upon these teachings it would have been obvious to one of ordinary skill in the art at the time of the invention to prepare and implant the dental implant of Morgan with the polymer layer having functional groups as taught by Chapman et al. via the method of Hawker et al. using an acrylate monomer coupled with tri(sarcosine) instead of the phosphorylcholine as taught by Zhang et al. (see instant claims 44-46). A free radical polymerization initiated from a self assembled monolayer of initiator-terminated alkanethiols on a gold surface would follow from this combination of references yielding the claimed stem and plurality of branches (see instant claim 28). Further modification of the resulting layer of polymer brush molecules by covalently attaching a protein (ligand), based upon the teachings of Chapman et al., would also have been obvious (see instant claims 18 and 50). The implantation of the device, as taught by Morgan, would result in its contacting blood for greater than one day. There would have been a reasonable expectation of success for the device to resist protein and bacterial adhesion for at the lower end of the implantation time taught by Morgan. Flynn et al. provide data that address the stability of alkanethiol self-assembled monolayers on gold that carry non-fouling terminal groups. After approximately 21 days in blood serum, the stability of the monolayer was compromised such that it lost much of its protein resistance (see page 10914 column 2 paragraph 1). As an embodiment based upon an alkanethiol self assembled monolayer, the artisan of ordinary skill would expect this method to be functional and enabled for the lower end of the implantation taught by Morgan based upon these teachings by Flynn et al.

Therefore claims 2, 4-7, 9, 11-14, 16, 18-19, 21, 28-31, 51 and 53 are obvious over Chapman et al. in view of Zhang et al., Hawker et al., Morgan and Flynn et al.

Claims 17 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chapman et al. in view of Zhang et al., Hawker et al., Morgan, and Flynn et al. as applied to claims 2, 4-7, 9, 11-14, 16, 18-19, 21, 28-31, 51 and 53 and further in view of Allbritton et al. and Leckband et al.

Chapman et al. in view of Zhang et al., Hawker et al., and Morgan make obvious the method of instant claim 28 where the device is an orthopedic device with an alkanethiol linking layer to which is attached a polymer brush composed of vinyl core monomers with tri(sarcosine) as head groups on its bristles (see instant claim 28). This modified reference does not explicitly teach the surface density of polymer.

Allbritton et al. teach surface grafted polymers to modify the surface of medical devices and confer desired properties (see paragraph 12). Particular monomers that resist protein adhesion are chosen for surface initiated polymerization (see paragraph 42). Allbritton et al. go on to teach various grafting densities for these monomers that include polyethylene glycol monomethoxyl acrylate (see paragraphs 34 and 42). Specifically, grafting densities from approximately 5 $\mu g/cm^2$ (50 mg/m^2) to 60 $\mu g/cm^2$ (600 mg/m^2) are taught (see figure 4A and paragraph 24; instant claim 17).

Leckband et al. teach polymer brushes on a substrate as a protein resistant surface (see abstract). In particular, Leckband et al. discuss that the graft density (polymer surface density) is a key parameter in controlling the degree of protein

adsorption retardation (see page 1143 paragraph 4). Leckband et al. also teach that this density is optimized based upon the target environment (e.g. size, geometry and concentration of proteins) (see page 1143 paragraph 4). Thus in view of the teachings of Allbritton et al. of polymers with functional groups that were taught by Chapman et al. to function similarly to tri(sarcosine), it would have been well within the purview of one of ordinary skill in the art to optimize the grafting density of the polymers of Chapman et al. in view of Zhang et al., Hawker et al., and Morgan based upon the teachings of Allbritton et al. Therefore claims 17 and 28 are obvious over Chapman et al. in view of Zhang et al., Hawker et al., Morgan, Flynn et al., Allbritton et al., and Leckband et al.

Claims 8 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chapman et al. in view of Zhang et al., Hawker et al., Morgan, and Flynn et al. as applied to claims 2, 4-7, 9, 11-14, 16, 18-19, 21, 28-31, 51 and 53 above, and further in view of Guan et al. (previously cited)

Chapman et al. in view of Zhang et al., Hawker et al., and Morgan make obvious the method of instant claim 28. This modified reference does not explicitly teach that the polymerization is carried out via atom transfer radical polymerization.

Guan et al. teach that although it is know to polymerize vinyl monomers via free radical polymerization, atom transfer radical polymerization is also a via means of polymerizing these same monomers (see column 1 lines 58-59 and column 2 lines 10-19). Thus as a known option within their technical grasp, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ atom transfer radical

polymerization as the polymerization method instead of free radical polymerization in the invention of Chapman et al. in view of Zhang et al., Hawker et al., and Morgan where vinyl monomers are used as the core group. Therefore claims 8 and 28 are obvious over Chapman et al. in view of Zhang et al., Hawker et al., Morgan, Flynn et al., and Guan et al.

Response to Arguments

Applicants' arguments, filed May 7, 2010, have been fully considered but they are moot in light of the new grounds of rejection. Nevertheless arguments against references that are cited in the current set of rejections are addressed.

Applicants argue that Hawker et al. and Zhang et al. teach opposite approaches. However, both of these references teach non-fouling coatings to reduce non-specific protein adhesion to surfaces via surface modification. In particular both utilize polymers with non-fouling side chains to confer reduced protein adhesion to surfaces. For this reason their teachings are compatible and one of ordinary skill would have found the teachings of one relevant to the other as well as to Chapman et al.

Applicants discuss of a statement made in Healy et al. that the stability of the alkanethiol monolayer *in vivo* had not been determined. This argument was persuasive in part, but the highlighting of this statement also raised questions about the stability of the instantly claimed product (which uses the same sort of alkanethiol monolayer) and is addressed in the rejection under 35 USC 112 first paragraph above.

In light of the amendment to the claims changing all of the product claims to method claims and applicants' arguments, all previously rejections are hereby withdrawn and new rejections are presented.

The rejections and/or objections detailed above are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CARALYNNE HELM whose telephone number is (571)270-3506. The examiner can normally be reached on Monday through Friday 9-5 (EDT).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Caralynne Helm/
Examiner, Art Unit 1615

/Juliet C Switzer/
Primary Examiner, Art Unit 1634